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(54) **COMPRIMES DE NAPROXENE A LIBERATION-RETARD**

(54) **CONTROLLED RELEASE NAPROXEN TABLETS**

(57) Comprimé pharmaceutique à libération contrôlée qui convient pour la posologie quotidienne contenant du naproxen et environ 3 pour cent en poids de HPMC ayant un poids moléculaire moyen en nombre d'environ 190 000.

(57) A controlled release pharmaceutical tablet suitable for daily dosing comprising naproxen and about 3 weight percent of HPMC having a number average molecular weight of about 190,000.

ABSTRACT

A controlled release pharmaceutical tablet suitable for daily dosing comprising naproxen and about 3 weight percent of HPMC having a number average molecular weight of about 190,000.

CONTROLLED RELEASE NAPROXEN TABLETS

Field of the Invention

The present invention relates to controlled release preparations of naproxen for oral administration. Specifically, it relates to a tablet comprising naproxen and hydroxypropylmethylcellulose (HPMC), which provides a release profile suitable for daily dosing.

Description of Related Art

Naproxen is a well known and widely used anti-inflammatory medication with analgesic and antipyretic properties. It is used for the relief of pain and inflammation generally, and for specific conditions such as arthritis and dysmenorrhea.

Hydroxpropylmethylcelluloses are commercially available in various grades, under several tradenames, including Methocel* E, F, J, and K (all previously designated as Methocel EG) from The Dow Chemical Co., U.S.A., HPM* from British Celanese, Ltd., England, and Metolose SH* from Shin-Etsu, Ltd., Japan. The various grades available under a given tradename represent differences in methoxy and hydroxypropoxyl content as well as molecular weight and viscosity. Commercial designations of the various HPMCs reflect their individual viscosity types and are based on the viscosities of 2% aqueous solutions at 20° C as determined according to the method described in the United States Pharmacopoeia, Rev. 23. The viscosities range from 15 cps to 100,000 cps and represent number average molecular weights of from about 10,000 to about 190,000. Each of the various grades under a given tradename is a HPMC of a single viscosity type, e.g. 50 cps, 100 cps, 4,000 cps, 15,000 cps, etc.

* trade-marks

The area of controlled release pharmaceuticals is increasingly important in the formulation, manufacture and marketing of new pharmaceutical products. The technologies and corresponding products of this art are variously described as, among others, sustained release, controlled release, prolonged action, depot, delayed action, retarded release, and timed release pharmaceuticals. In describing the present invention, the term "controlled release" is used to indicate that control is exercised over the duration and profile of the in vivo drug release curve.

Controlled release drug dosage forms offer many advantages over conventional dosage forms for particular drugs. Of major importance both practically and therapeutically is the decrease in frequency of administration required to achieve the desired effect. A dosage form which is taken only once-a-day greatly improves patient compliance, and by extending the drug's activity through the night, permits the patient to sleep undisturbed until the morning. By enhancing the acceptability of a medication regime, patient compliance, and hence therapy, is improved.

Another important therapeutic advantage of controlled release drug dosage forms is a reduction in the fluctuation of plasma drug concentrations.

Conventional immediate-release dosage forms of naproxen are administered two or three times daily in order to maintain therapeutic blood levels, and to minimize the differential between peak and trough blood levels during multiple dose therapeutic regimens. Peak to trough blood level ratios of about 2:1 are generally achieved with these regimens. In the interest of maximizing the therapeutic effectiveness of the drug, it is desirable to minimize as much as possible the ratio of peak to trough blood levels obtained during multiple dose therapy. Controlled release formulations generally permit less frequent dosing intervals to obtain acceptable peak to trough ratios.

Many different types of controlled release oral dosage forms have been developed, but each has disadvantages which affect its suitability to a particular drug and therapeutic objective. Wide variations in the chemical and pharmacokinetic properties of different drugs impose such varied requirements on the design of controlled drug delivery formulations, that formulations which are suitable for one drug cannot generally be predictably applied to other drugs. A formulation which incorporates the drug in a soluble or erodible matrix is desirable due to its ease of manufacture, low incidence of lot to lot variability, and relative low cost. The use of hydrophilic gums such as HPMC as sustained release matrix materials is known and has been demonstrated with a variety of active agents.

Christenson and Dale (U.S. Pat. No. 3,065,143) disclosed the use of certain hydrophilic gums, including HPMC, as carrier base materials in the preparation of sustained release pharmaceutical tablets. The tablets consisted essentially of a mixture of a drug in combination with at least one-third part by weight of the hydrophilic gum.

Schor and Nigalaye (U.S. Pat. No. 4,369,172, 1983) have disclosed the use of certain HPMCs for "prolonged release therapeutic compositions." In that case, the carrier base is low viscosity HPMC having a number average molecular weight below 50,000 and a hydroxypropyl content of 9-12%. Specifically cited as examples corresponding to these criteria are Methocel* E50 and Metolose* 60HS50, which are 50 cps viscosity grade HPMCs having number average molecular weights in the range of 23,000. Examples 1-4 describe tablets consisting essentially of about 57% by weight of one or the other of these two materials in combination with lithium carbonate. The tablets weigh about 700 mg and release the active agent for up to 14 hours in vitro.

Further examples in U.S. Pat. No. 4,369,172 show tablets containing 16-20% by weight of the polymer.

* trade-marks

The Dow Chemical Company publishes a brochure entitled "Formulating for Controlled Release with Methocel Premium Cellulose Ethers" which describes the various commercially available Methocel® polymers, identifying their relative viscosities, rates of hydration and gel strength properties. The brochure also gives guidance for formulating sustained release pharmaceutical products.

Canadian Patent 1204671 discloses a controlled release tablet for a daily oral administration in the form of a matrix comprising about 4 to 9 weight per cent of HPMC having a number average molecular weight in the range of from about 80,000 to about 130,000. In the compositions of Canadian Patent 1204671, the HPMC acts both as an agent to control the rate of release of the naproxen and as a binder to enable formulation of a tablet of sufficient hardness.

While the concept of utilizing HPMC in oral dosage forms to prolong the rate of release of drugs into the blood stream is known, and prolonged release of various active agents from such dosage forms has been demonstrated, the art available to formulate oral controlled release forms of naproxen has certain disadvantages. First, it is apparent from the foregoing discussion of the relevant art that presently known sustained release tablet formulations rely on levels of HPMC of at least about 4 percent by weight to achieve adequate duration of drug release. A problem with using any of these formulations is the additional bulk of the resulting tablet. There is an approximate upper limit to the tablet bulk that will be tolerated by the patient. This limit varies from patient to patient, but can be as low as 650 mg. Thus, with drugs such as naproxen, for which the therapeutic dosage range is 500-1000 mg/day, the additional tablet bulk which is created by inclusion of substantial amounts of matrix material will render the tablets unacceptable to many patients.

Additionally, HPMC is relatively expensive, and the inclusion of an excessive quantity increases the cost of the composition.

Description of the Invention

The present invention is a controlled release tablet for once-daily oral administration of 500-1000 mg of naproxen which is formed as a matrix comprising, in addition to naproxen, about 3 weight percent of HPMC having a number average molecular weight of about 190,000.

It has been surprisingly found that a tablet exhibiting both an adequately-slow rate of release and an adequate hardness can be achieved using HPMC at a level of only about 3 weight percent, provided that the HPMC that is used has a number average molecular weight of about 190,000, and provided that it is incorporated into the matrix with naproxen in a wet granulation process, as explained further hereinafter.

The tablet matrix preferably further includes a minor amount of a pharmaceutically acceptable lubricant such as magnesium stearate to aid in the process of making tablets. This amount will vary between about 0.1 to 3% generally, and preferably represents about 1% of the total weight of the tablet. Suitable lubricants include magnesium stearate, stearic acid, calcium stearate and the like, or mixtures thereof. Magnesium stearate is preferred.

Optionally, the tablet matrix may include minor amounts of other pharmaceutically acceptable excipients, such as colorants and glidants. Suitable colorants include, but are not limited to, yellow #6 lake pigment, and generally represent 1% or less of the tablet weight. Suitable glidants include, but are not limited to, pharmaceutical grades of talc and fused silica.

In accordance with the present invention, the amount of naproxen that is incorporated in a tablet may range between about 500 and about 1000 mg. The therapeutic range of about 500 - 1000 mg per tablet is indicated for the treatment of pain of arthritis, dysmenorrhea and other conditions. The tablet of the present invention provides a release period suitable for once-daily dosing, i.e. once within a 24-hour period.

release period suitable for once-daily dosing, i.e. once within a 24-hour period. Naproxen is generally administered at levels of 500, 750, or 1000 mg/day, depending on the physician's judgement of the needs of the patient.

HPMC is a water soluble cellulose ether, and is commercially available in various grades under the tradenames mentioned about in the DESCRIPTION OF RELATED ART. The physicochemical properties of these polymers vary over a wide range.

The number average molecular weight (Mn) of the hydroxypropyl methylcellulose is the sum of the individual molecular weights of a representative sample population of molecules divided by the number of molecules in that sample. Compositions of this invention use HPMC having number average molecular weight of about 190,000.

Hydroxpropylmethylcellulose which has number average molecular weight of about 190,000 is available as a single viscosity type polymer. As used herein, the term "single viscosity type" refers to commercially available grades of HPMC whose commercial designations reflect their individual viscosity type. A single viscosity type HPMC suitable for use in the present invention is Methocel® Premium K100M (Dow Chemical Co., U.S.A.) which is a 100,000 cps viscosity polymer having number average molecular weight of about 190,000.

The controlled release tablet of the present invention provides therapeutic blood levels of naproxen for at least 24 hours, and is thus suitable for once-daily administration. Fluctuations in blood levels during multi-dose therapeutic regimens are minimized by the tablets of the present invention, such that the ratio of mean peak plasma concentration to mean trough plasma concentration is 2:1 or lower.

The following example serves to further illustrate the invention, but is not to be interpreted as limiting the scope of the appended claims in any way:

EXAMPLE

Sustained Release Naproxen Tablets, 750 mg

Tablets were prepared from the following ingredients:

	Ingredients		mg/tablet
1	naproxen		750.0
2	HPMC (Methocel K100M)	24.0	
3	colorants		3.0
4	water		200.0
5.	magnesium stearate		3.0

TOTAL WEIGHT is 780 mg per tablet excluding the water.

The process used was as follows: The naproxen, Methocel® K100M and colorants were well blended, and then granulated with the water. The granulation was tray-dried in a 65° C oven for 12 hours, passed through a #20 screen, and then mixed with the magnesium stearate. The resulting material was compressed into tablets of weight 780 mg.

The tablets of this example were found to have good hardness. Furthermore, the tablets were found to exhibit release rate comparable to commercially available naproxen controlled release tablets sold under the tradename Naprosyn® SR

As used herein, the term "about 3" when used in relation to the weight percent of HPMC is intended to mean between 2 and 3.6. Also, as used herein the term "about 190,000" when used in relation to number average molecular weight is intended to mean between 150,000 and 230,000.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A controlled release tablet for once-daily oral administration of naproxen, said tablet comprising, in addition to naproxen, from 2 to 3.6 weight percent of HPMC having a number average molecular weight of from 150,000 to 230,000.

2. The controlled release tablet of Claim 1 which further comprises from 0.1 to 3 weight percent of a pharmaceutically acceptable lubricant.

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